FORM PTO-1390 (REV. 11-2000) — U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
3920-0110P	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
10/089846 (NEW)	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/03770	October 2, 2000	October 4, 1999

TITLE OF INVENTION
PHARMACEUTICAL COMPOSITIONS AND THEIR USE IN THE TREATMENT OF NEOPLASTIC DISEASE

APPLICANT(S) FOR DO/EO/US
CARTER, John

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). (WO 01/24803)
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is transmitted herewith.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 20. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form PTO-1449(s), and International Search Report (PCT/ISA/210) with 7 cited document(s).
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)
20. ☒ Other items or information:
    1.) PCT/IPEA/409
    2.) Three (3) Sheets of Formal Drawings

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
NEW 10/089846	PCT/GB00/03770	3920-0110P

21. ☒ The following fees are submitted		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):			
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1,040.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.	$740.00		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4).	$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	34 - 20 =	14	X $18.00	$ 252.00	
Independent Claims	10 - 3 =	7	X $84.00	$ 588.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		NONE	+ $280.00	$ 0	
TOTAL OF ABOVE CALCULATIONS =				$ 1,860.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2				$ 0	
SUBTOTAL =				$ 1,860.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0	
TOTAL NATIONAL FEE =				$ 1,860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0	
TOTAL FEES ENCLOSED =				$ 1,860.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ **1,860.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

Date: April 4, 2002

By _____
James W. Hellwege, #28,808

/nv

PATENT
3920-0110P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: John CARTER

Serial No. Unassigned
(National Phase of PCT/GB00/03770)

Filed: April 4, 2002

For: PHARMACEUTICAL COMPOSITIONS AND THEIR USE IN THE TREATMENT OF NEOPLASTIC DISEASE

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

April 4, 2002
Thursday

Dear Sir:

Prior to examination of the above application, please amend the application as follows:

IN THE SPECIFICATION:

Page 1, preceding line 1, insert the following:

- - This application is a national stage application of PCT application PCT/GB00/03770, filed October 2, 2002, claiming priority of UK application No. 9923431.2, filed October 4, 1999, and UK application No. 0014420.4, filed June 13, 2000. - -

IN THE CLAIMS:

Cancel claims 2-20 without disclaimer or prejudice.

[redacted]

Amend claim 1 as follows:

1. (Amended) A composition comprising as the sole pharmacologically active components:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) a source of salicylic acid a physiologically acceptable derivative thereof;

(c) vitamin C and, optionally, one or more of:

(d) a physiologically acceptable source of assimilable manganese;

(e) a physiologically acceptable source of assimilable iron;

(f) a physiologically acceptable source of assimilable sulphur; and

(g) a physiologically acceptable source of assimilable zinc.

Add the following new claims:

- - 21. The composition according to Claim 1 comprising as the sole pharmacologically active components:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof; and

(c) vitamin C.

22. The composition according to Claim 1, containing (e) a physiologically acceptable source of assimilable iron and (f) a physiologically acceptable source of assimilable sulphur.

23. The composition according to Claim 1, containing a physiologically acceptable source of assimilable zinc.

[redacted]

24. The composition according to Claim 1, wherein the said metals are present in the form of salts with organic or inorganic acids.

25. The composition according to Claim 24, wherein the salts are the same or different and are selected from the group consisting of orotates, aspartates, gluconates, tartrates, citrates, lactates and acetates.

26. The composition according to Claim 25, wherein the copper salt is selected from the group consisting of copper gluconate and copper orotate and the manganese salt, if present, is selected from the group consisting of manganese gluconate and manganese orotate.

27. The composition according to Claim 24, wherein the salts are the same or different and are selected from the group consisting of chlorides, bromides, iodides, phosphates and sulphates.

28. The composition according to Claim 1, wherein component (b) is sodium salicylate.

29. A composition comprising:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof;

(c) vitamin C; and

(d) a physiologically acceptable source of assimilable manganese.

30. The composition according to Claim 29, containing (e) a physiologically acceptable source of assimilable iron and (f) a physiologically acceptable source of assimilable sulphur.

31. The composition according to Claim 29, containing a physiologically acceptable source of assimilable zinc.

32. The composition according to Claim 29, wherein the said metals are present in the form of salts with organic or inorganic acids.

33 The composition according to claim 32, wherein the salts are the same or different and are selected from the group consisting of orotates, aspartates, gluconates, tartrates, citrates, lactates and acetates.

34. A composition according to Claim 33, wherein the copper salt is selected from the group consisting of copper gluconate and copper orotate and the manganese salt, if present, is selected from the group consisting of manganese gluconate and manganese orotate.

35. The composition according to claim 32, wherein the salts are the same or different and are selected from the group consisting of chlorides, bromides, iodides, phosphates and sulphates.

36. The composition according to Claim 29, wherein component (b) is sodium salicylate.

37. A composition comprising:

15 to 60 parts by weight copper gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper gluconate is used;

300 to 600 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or another alkali or alkaline earth metal salt thereof other than sodium salicylate is used; and

200 to 1000 parts by weight vitamin C,

the parts by weight referred to being based on the total weight of these ingredients in the composition.

38. The composition according to Claim 37 comprising:

15 to 40 parts by weight copper gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper gluconate is used;

300 to 400 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or another alkali or alkaline earth metal salt thereof other than sodium salicylate is used; and

300 to 500 parts by weight vitamin C.

39. The composition according to Claim 37, further comprising 15 to 60 parts by weight manganese gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than manganese gluconate is used.

40. The composition according to Claim 37, further comprising 15 to 60 parts by weight iron gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable iron other than iron gluconate is used, and 15 to 60 parts by weight of sulphur.

41. The composition according to Claim 37, further comprising 15 to 60 parts by weight zinc gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc gluconate is used.

42. The composition according to Claim 37, comprising:

(a) 15 to 40 parts by weight copper gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper gluconate is used;

(b) 350 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or another alkali or alkaline earth metal salt thereof other than sodium salicylate is used; and

(c) 400 parts by weight vitamin C.

43. The composition according to Claim 42, further comprising 15 to 40 parts by weight manganese gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than manganese gluconate is used.

44. The composition according to Claim 42, further comprising 15 to 40 parts by weight iron gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable iron other than iron gluconate is used, and 15 to 40 parts by weight of sulphur.

[redacted]

45. The composition according to Claim 42, further comprising 15 to 40 parts by weight zinc gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc gluconate is used.

46. A composition comprising as the sole pharmacologically active components:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof;

(c) vitamin C and, optionally, one or more of:

(d) a physiologically acceptable source of assimilable manganese;

(e) a physiologically acceptable source of assimilable iron;

(f) a physiologically acceptable source of assimilable sulphur; and

(g) a physiologically acceptable source of assimilable zinc,

wherein the composition is in the form of an orally administrable unit dosage form.

47. A composition comprising:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof;

(c) vitamin C; and

(d) a physiologically acceptable source of assimilable manganese,

wherein the composition is in the form of an orally administrable unit dosage form.

[redacted]

48. A composition comprising as the sole pharmacologically active components:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof;

(c) vitamin C and, optionally, one or more of:

(d) a physiologically acceptable source of assimilable manganese;

(e) a physiologically acceptable source of assimilable iron;

(f) a physiologically acceptable source of assimilable sulphur; and

(g) a physiologically acceptable source of assimilable zinc,

for use in the treatment of the human or animal body by therapy.

49. A composition comprising:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof;

(c) vitamin C; and

(d) a physiologically acceptable source of assimilable manganese,

for use in the treatment of the human or animal body by therapy.

50. A method of treating or preventing neoplastic disease in a human or animal patient comprising administering to the patient an anti-neoplastic effective amount of a composition comprising:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof; and

(c) vitamin C.

[redacted]

51. A method of treating or preventing neoplastic disease in a human or animal patient according to Claim 50 further comprising (d) a physiologically acceptable source of assimilable manganese.

52. A pharmaceutical product containing a composition comprising as the sole pharmacologically active components:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof;

(c) vitamin C and, optionally, one or more of:

(d) a physiologically acceptable source of assimilable manganese;

(e) a physiologically acceptable source of assimilable iron;

(f) a physiologically acceptable source of assimilable sulphur and

(g) a physiologically acceptable source of assimilable zinc; and

an additional component selected from the group consisting of vitamin C in addition to that in the composition, one or more amino acids and nicotinic acid, as a combined preparation for simultaneous, separate or sequential use in the treatment of a neoplastic disease.

53. A pharmaceutical product containing a composition comprising:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) salicylic acid or an alkali or alkaline earth metal salt thereof;

(c) vitamin C; and

(d) a physiologically acceptable source of assimilable manganese, and

an additional component selected from the group consisting of vitamin C in addition to that in the composition, one or more amino acids and nicotinic acid, as a combined preparation for simultaneous, separate or sequential use in the treatment of a neoplastic disease.- -

REMARKS

Claim 1 is amended and claims 2-20 replaced by new claims 21-53. No new matter is added by this amendment. The specification is amended to identify the priority applications.

The application is now believed to be in condition for allowance and an early indication of same is earnestly solicited.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Very truly yours,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____

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CLAIM AMENDMENTS WITH MARKINGS TO SHOW CHANGES

1. (Amended) A composition comprising as the sole pharmacologically active components:

(a) a physiologically acceptable source of assimilable copper other than a copper salicylate complex;

(b) a source of salicylic acid [or an alkali or alkaline earth metal salt thereof] a physiologically acceptable derivative thereof; [and];

(c) vitamin C and, optionally, one or more of:

(d) a physiologically acceptable source of assimilable manganese;

(e) a physiologically acceptable source of assimilable iron;

(f) a physiologically acceptable source of assimilable sulphur; and

(g) a physiologically acceptable source of assimilable zinc.

PHARMACEUTICAL COMPOSITIONS AND THEIR USE

This invention relates to pharmaceutical compositions and their use in the treatment of neoplastic disease.

There has long been a demand for a safe and effective treatment of neoplastic disease. WO 84/04922 proposes the use of copper salicylate complexes for this purpose. However, the copper salicylate complexes of WO 84/04922 are not sufficiently effective to be put to widespread use.

It has now unexpectedly been discovered that a composition comprising an assimilable copper compound, a source of salicylic acid or a derivative thereof and vitamin C, is particularly effective in the treatment of neoplastic disease.

The present invention therefore provides a composition comprising:

(a) a physiologically acceptable source of assimilable copper;

(b) a source of salicylic acid or a physiologically acceptable derivative thereof; and

(c) vitamin C.

Addition of vitamin C to components (a) and (b) leads to a synergistic increase in effectiveness.

Preferably, the composition of the invention further comprises (d), a physiologically acceptable source of assimilable manganese. Alternatively, the composition of the invention may further comprise (e), a physiologically acceptable source of assimilable iron or (f), a physiologically acceptable source of assimilable sulfur. Compositions of the invention comprising both (e) and (f) are particularly preferred.

Particularly preferred compositions of the invention are those comprising:

(a) a physiologically acceptable source of assimilable copper;

(b) a source of salicylic acid or a physiologically acceptable derivative thereof;

(c) vitamin C;

(d) a physiologically acceptable source of assimilable manganese;

(e) a physiologically acceptable source of assimilable iron; and

(f) a physiologically acceptable source of assimilable sulfur.

It has also unexpectedly been found that compositions of the invention further comprising a physiologically acceptable source of assimilable zinc are particularly effective in the treatment of sarcomas.

The present invention therefore also provides a composition of the invention, further comprising a physiologically acceptable source of assimilable zinc.

The sources of copper, manganese, iron and zinc used in the composition of the present invention preferably contain the metals in ionic form, e.g. as salts with organic or inorganic acids. However, other metal compounds which provide assimilable sources of the metals, e.g. metal oxides, can also be used.

Thus, a physiologically acceptable source of assimilable copper is typically a copper oxide or a salt of copper with an organic or inorganic acid. A physiologically acceptable source of assimilable manganese is typically a manganese oxide or a salt of manganese with an organic or inorganic acid. A physiologically acceptable source of assimilable iron is typically an iron oxide or a salt of iron with an organic or inorganic acid. A physiologically acceptable source of assimilable zinc is typically a zinc oxide or a salt of zinc with an organic or inorganic acid.

Suitable physiologically acceptable salts of the above metals with organic acids include salts with orotic acid, aspartic acid, gluconic acid, tartaric acid, citric acid, lactic acid, acetic acid, fumaric acid, maleic acid, malic acid, ascorbic acid, succinic acid, benzoic acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid and p-toluenesulphonic acid . Suitable physiologically acceptable salts of the above metals with inorganic acids include salts with hydrochloric acid, hydrobromic acid, hydriodic acid, phosphoric acid, diphosphoric acid, nitric acid or sulfuric acid, preferably hydrochloric, hydrobromic, hydroiodic, phosphoric or sulfuric acid. Such salts are available commercially or may be prepared if desired by known methods.

Preferred physiologically acceptable salts are salts with organic acids, more preferably salts with orotic acid, aspartic acid, gluconic acid, tartaric acid, citric acid, lactic acid or acetic acid and most preferred are salts with orotic or gluconic acid.

It is also preferred that the physiologically acceptable salts are water soluble, for example salts with gluconic acid.

It is particularly preferred that the physiologically acceptable salt of assimilable copper is copper orotate or copper gluconate, most preferably copper gluconate. It is particularly preferred that the physiologically acceptable salt of assimilable manganese is manganese orotate or manganese gluconate, most preferably manganese gluconate. It is particularly preferred that the physiologically acceptable salt of assimible iron is iron orotate or iron gluconate, most preferably iron gluconate. It is particularly preferred that the physiologically acceptable salt of assimilable zinc is zinc orotate or zinc gluconate, most preferably zinc gluconate.

When, as is preferred, the compositions of the invention contain more than one metal, all the metal salts preferably include the same anion. This anion is typically orotate or gluconate, preferably gluconate.

The source of salicylic acid or a physiologically acceptable derivative thereof is typically salicyclic acid or a physiologically acceptable derivative thereof. Typically, the said derivative is a compound in which the carboxyl or hydroxyl function of salicylic acid has been converted into a derivative.

A physiologically acceptable derivative of salicyclic acid is typically a salicylic acid metal salt, ester or amide. Examples of suitable metal salts include alkali metal salts, for example sodium and potassium salts, and alkaline earth metal salts, for example calcium and magnesium salts. Sodium salicylate is most preferable.

Examples of suitable esters include C_{1-6} alkyl esters, for example methyl, ethyl, propyl, butyl, pentyl or hexyl esters and particularly preferred are the methyl and ethyl esters. Examples of suitable amides are amides obtainable by reacting salicylic acid with an amine HNR_1R_2, wherein R_1 and R_2 may be the same or different and are selected from hydrogen and C_{1-6} alkyl groups such as methyl, ethyl, propyl, butyl, pentyl or hexyl. R_1 and R_2 are preferably selected from hydrogen, methyl and ethyl and most preferably both R_1 and R_2 are hydrogen.

Derivatives in which both the hydroxyl function and the carboxyl function of salicylic acid have been converted into a derivative can also be used.

When the hydroxyl function of salicyclic acid is converted to a derivative it is typically converted to an ester, for example a C_1-C_6 alkyl ester such as acetyl-salicylic acid (aspirin).

A particularly preferred derivative of salicylic acid is sodium salicylate.

Salicylic acid itself and suitable derivatives of it are commercially available.

Components (a) and (b) may be present in the composition of the invention as a copper salicylate complex. As used herein, a copper salicylate complex is a complex of copper and salicylic acid or a complex of copper and a said physiologically acceptable derivative of salicylic acid.

Typically, the physiologically acceptable source of assimilable sulfur is elemental sulfur and any allotropic form of sulfur may be used. Preferably, sulfur is present in the composition in the form of sublimed sulfur or precipitated sulfur, most preferably sublimed sulfur.

The compositions of the invention typically comprise 15 to 60, preferably 25 to 40, parts by weight copper gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper gluconate is used.

Typically, the compositions of the invention comprise from 300 to 600, preferably 300 to 400, most preferably 350, parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other than sodium salicylate is used.

Typically, the compositions of the invention comprise from 200 to 1000, preferably 300 to 500, most preferably 400, parts by weight vitamin C. Preferably, vitamin C is present in the compositions of the invention in an amount significantly larger than that which is regarded as the normal minimum daily requirement for an adult.

Typically, the compositions of the invention containing a physiologically acceptable source of assimilable manganese, comprise from 15 to 60, preferably 25 to 40, parts by weight manganese gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than manganese gluconate is used.

Typically, the compositions of the invention containing a physiologically acceptable source of assimilable iron, comprise from 15 to 60, preferably 25 to 40, parts by weight iron gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable iron other than iron gluconate is used.

Typically, the compositions of the invention containing a physiologically acceptable source of assimilable sulfur, comprise from 15 to 60, preferably 25 to 40, parts by weight sulfur.

Typically, the compositions of the invention containing a physiologically acceptable source of assimilable zinc, comprise from 15 to 60, preferably 25 to 40, parts by weight zinc gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc gluconate is used.

The parts by weight referred to are based on the total weight of these ingredients in the composition.

The amounts of the active ingredients in the compositions of the invention should be calculated having regard to the intended dosage to be administered. When the composition is to be administered orally, as is usual, a suitable dosage is about 2ml volume for each 60 lbs of body weight of the subject to be treated. This dosage can be administered up to three times a day. The 2ml volume dosage typically contains from 8 to 35 mg, preferably from 14 to 25 mg of copper gluconate, or an equivalent amount of active ingredient when a physiologically acceptable source of copper other than copper gluconate is used. The 2ml volume dosage typically contains from 170 to 350 mg, preferably from 170 to 230 mg and most preferably about 200 mg sodium salicylate or an equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other than sodium salicylate is used. The 2ml volume dosage typically contains from 110 to 570 mg, preferably from 170 to 285 mg and most preferably about 230 mg vitamin C.

A suitable dosage of about 2 ml volume of the compositions of the invention comprising a physiologically acceptable source of assimilable manganese, typically contains from 8 to 35 mg, preferably from 14 to 25 mg of manganese gluconate or an

equivalent amount of active ingredient when a physiologically acceptable source of manganese other than manganese gluconate is used.

A suitable dosage of about 2 ml volume of the compositions of the invention comprising a physiologically acceptable source of assimilable iron typically contains from 8 to 35 mg, preferably from 14 to 25 mg of iron gluconate or an equivalent amount of active ingredient when a physiologically acceptable source of iron other than iron gluconate is used.

A suitable dosage of about 2ml volume of the compositions of the invention comprising a physiologically acceptable source of assimilable sulfur typically contains from 8 to 35 mg, preferably from 14 to 25 mg of sulfur.

A suitable dosage of about 2 ml volume of the compositions of the invention comprising a physiologically acceptable source of assimilable zinc typically contains from 8 to 35 mg, preferably from 14 to 25 mg of zinc gluconate or an equivalent amount of active ingredient when a source of zinc other than zinc gluconate is used.

These figures are approximate and considerable variation in the proportions of the active ingredients is possible without losing the valuable properties of the compositions.

The compositions of the invention may be made by first forming an intimate mixture of the metals to be used in the form of suitable salts or other derivatives, together with sulfur, if present. This mixture in finely ground form can then be added to an aqueous solution or suspension of the salicylic acid or derivative thereof. Typically, from 2 to 5 ml, preferably about 3½ ml of aqueous solution or suspension is used. This solution preferably contains 5-20%, preferably about 10%, by weight of salicylic acid or derivative. The vitamin C may be added before or after the salicylic acid solution, and is preferably added before the salicylic acid solution such that all of the solid ingredients are combined first. The resulting slurry or solution may be administered orally.

The compositions of the invention are thought to work by promoting the formation of the enzyme superoxide dismutase (SOD). SOD functions as a free radical scavenger and reduces DNA damage caused by free radical attack.

The compositions of the invention may be used in human and veterinary

medicine, for example in the treatment of cats and dogs. They are useful in the treatment or prevention of a neoplastic disease. They are capable of improving the condition of a patient suffering from a cancer.

Typically, a human or animal is treated by initially administering said dosage of 2 ml of the composition of the invention, comprising active ingredients in the amounts set out above, in the form of an aqueous solution or suspension, per 60 lbs body weight of subject followed by a half dose of a similar solution or suspension 1 to 2 hours later. Four hours later a further half dose may be given. Subsequent treatment (when the tumour has noticeably regressed and/or the symptoms have been considerably alleviated) may consist of the oral administration of 2 ml of the said solution or suspension per 60 lbs body weight of subject once a day. This may be given for three weeks, then, if further progress has been made, the dose may be reduced to 2 ml per 60 lbs body weight on alternate days for 3 weeks. The frequency of dosing may be further reduced as further progress is made.

The compositions of the invention have been found effective in treatment of carcinomas of the breast, rectum, bladder, liver, peritoneum, stomach and urethra, and in some lymphomas. Compositions of the invention comprising a physiologically acceptable source of assimilable zinc are effective against sarcomas. The treatment may be continued until there is a marked regression in the size of the tumour or until the tumour disappears.

The compositions of the invention are normally administered orally. Preferably, therefore they are suitable for oral administration. Suitable forms for oral administration include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred forms for oral administration are tablets and capsules. However, other routes of administration may be possible provided suitable precautions are taken to make the compositions suitable for administration in the contemplated way. For example, the compositions of the invention may be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques, or as a suppository.

It has been found that the effectiveness of the compositions of the invention

can be enhanced if they are administered in conjunction with a dietary regime which is low in salt and high in potassium and essential amino acids such as proline, serine, glutamine, lysine, histidine, alanine, methionine and leucine. By way of example, vegetables and fruit may be mentioned as foods which have high potassium content. Porridge oats, for example, have a high potassium, low salt content. By way of example, liver may be mentioned as a food source rich in essential amino acids. Typically, for a human patient about 2 oz of liver per day has been found to be sufficient.

It has been found also that better results are obtained by supplementing the diet of a subject with additional vitamin C, i.e. vitamin C in addition to that preferably contained in the compositions of the invention. For example, the administration of 1 g of vitamin C per 20 lbs subject body weight per day, has been found to enhance the activity of the new compositions. Likewise, administration of nicotinic acid, for example 25 mg per 14 lbs subject body weight per day, has been found to give rise to improved activity of the compositions of the invention.

The following Examples illustrate the invention.

EXAMPLE 1

Copper (II) orotate (35 mg) and manganese (II) orotate (35 mg), in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 2

Copper (II) orotate (35 mg), manganese (II) orotate (35 mg) and zinc orotate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 3

To copper (II) orotate (35 mg) in finely divided form was added sodium salicylate solution (3.5 ml of a 10% aqueous solution) followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 4

Copper (II) orotate (35 mg), manganese (II) orotate (35 mg), iron (II) orotate (35 mg) and sublimed sulfur (35 mg), in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 5

Copper (II) orotate (35 mg), manganese (II) orotate (35 mg), iron (II) orotate (35mg), sublimed sulfur (35mg) and zinc orotate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added followed by

vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 6

Copper (II) gluconate (35 mg),vitamin C (400 mg) and manganese (II) gluconate (35 mg), in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added. The resulting solution is suitable for immediate oral administration.

EXAMPLE 7

Copper (II) gluconate (35 mg), vitamin C (400 mg), manganese (II) gluconate (35 mg) and zinc gluconate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added. The resulting solution is suitable for immediate oral administration.

EXAMPLE 8

To copper (II) gluconate (35 mg) and vitamin C (400 mg) in finely divided form was added sodium salicylate solution (3.5 ml of a 10% aqueous solution). The resulting solution is suitable for immediate oral administration.

EXAMPLE 9

Copper (II) gluconate (35 mg), vitamin C (400 mg), manganese (II) gluconate (35 mg), iron (II) gluconate (35 mg) and sublimed sulfur (35 mg), in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added. The resulting suspension is suitable for immediate oral administration.

EXAMPLE 10

Copper (II) gluconate (35 mg), vitamin C (400 mg), manganese (II) gluconate (35 mg), iron (II) gluconate (35mg), sublimed sulfur (35mg) and zinc gluconate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of

sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added. The resulting suspension is suitable for immediate oral administration.

EXAMPLE 11

This experiment was conducted at University College London under Home Office License. In this experiment 100 C57B1 male mice were injected subcutaneously with a transplantable RMA thymoma tumour. 50 of the mice were used as controls and 50 mice were experimental mice.

Mice have a much faster rate of metabolism than larger mammals. It was therefore decided to give the mice a larger dose of the formula than the dose which would be suitable for larger animals such as cats and dogs. This latter dose was accordingly increased by a factor of 10.

For a 30 g mouse, 0.022 ml of the solution prepared in Example 1 was administered. This was administered to the mice three times a day at 10 am, 3 pm and 6 pm. The composition was administered by gavage. In addition the experimental mice were fed on a diet of organic wheat, barley, oats and rye.

The general condition of the experimental and control mice following tumour injection is shown in Table 1.

Table 1

RMA thymoma in C57B1 male mice		
Days after Tumour injection	**Control**	**Experimental**
16	All mice have tumours. 2 killed because of large tumour size.	20/22 with palpable tumours. 2 probably have deep tumours. 1 sick mouse killed.
18		3 mice died as a result of treatment. 2 with small tumours. 1 had only a large lymph node.
20	4 mice killed with large tumours.	2 sick mice killed, both had tumours.
21	Remaining mice killed because of large tumours. All tumours firm and infiltrating muscle of thigh or peritoneal wall.	4 killed with large infiltrating tumours.
23		3/12 mice had superficial freely mobile plaque like tumours.
25		6 mice killed because of large tumour size. All tumours firm and infiltrating. 1 mouse had an axillary abscess.
29		4/6 remaining tumours fixed. Large lymph nodes palpable.
31		Remaining mice killed. 5/6 tumours infiltrating deeply. 1/6 more superficial but draining node grossly enlarged.

The growth of the tumour in experimental and control mice is shown in Figure 1. The weights of the experimental and control mice are shown in Figure 2.

The growth of the thymoma tumour was measured by callipers, i.e. the diameter of the surface of the tumour was determined. The tumours were not

weighed at the end of the experiment.

As can be seen from Figure 1, 21 days after tumour injection the tumours in the control mice were approximately 1.9 times larger than those in the experimental mice.

Apart from deaths caused by the stress of gavage, to which the control mice were not subjected, the only side effect observed was slight weight loss, probably attributable to the change of diet.

EXAMPLE 12

This experiment was conducted at University College London under Home Office License. Transplantable mammary carcinomas were injected into 100 male Balb/c mice. 50 of the mice were used as controls and 50 mice were experimental mice.

These tumours grew much more slowly than the thymomas injected in Example 11. Accordingly, less treatment was given to the experimental mice; they were gavaged only once a day with 0.22 ml of the solution prepared in Example 1 and fed on a diet of organic grains as described in Example 11. Nevertheless a result was obtained as can be seen from Figure 3 showing the growth of the mammary carcinoma in experimental and control mice. But because they were given less treatment the difference in growth rate between the experimental and control groups is much less than that observed in Example 11.

The tumours in the control group were only 1.14 times larger than in the experimental group at 23 days after tumour injection. However, 29 days after tumour injection the tumours in the control group were 1.19 times larger than the tumours in the experimental group.

Apart from deaths caused by the stress of gavage, to which the control mice were not subjected, the only side effect observed was slight weight loss, probably attributable to the change of diet.

EXAMPLE 13

Professor Peter Beverley of the Department of Oncology at University College London Medical School stated that although there was a statistically higher significant effect in tumour growth between the experimental and control mice in Examples 11 and 12, it was clear that the treatment by repeated gavage was stressful so that untreated mice were not a perfect control.

It was therefore decided that a further experiment should be performed but that this time the formula should be administered in the drinking water and given to the mice by gavage only once a day. As a water soluble copper salt was required for addition to the drinking water, it was decided to use copper gluconate in place of copper orotate. The control mice would also have the same organic grains diet as the experimental mice and be gavaged with water once a day. It was also decided that the experimental mice should be given extra vitamin C by having the vitamin C added to their drinking water.

This experiment was conducted at University College London under Home Office License.

Copper (II) gluconate, 35 mg, and manganese (II) orotate, 35 mg, in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added followed by vitamin C (400 mg).

The vitamin C was added to the drinking water of the experimental mice by putting 300 mg of vitamin C in 50 ml of water three times a day. Thus each cc contained 6 mg vitamin C. Each mouse drank on average 4 ml of water containing 24 mg of vitamin C three times a day. So each mouse received on average 72 mg of vitamin C per day.

50 C57B1 male mice were injected subcutaneously with a transplantable thymoma. 24 mice, the experimental mice, were treated, and 26 mice were used as a control.

It was decided to give the mice a larger dose of the formula because they would be gavaged only once a day and it was not sure how much drinking water each mouse would drink.

The dose per mouse compared to larger mammals was now increased by a

factor of 17.

Each mouse was gavaged with 0.04 ml of the composition prepared above once a day.

0.5 ml of the composition prepared above was added to the drinking water three times a day. 50 ml of drinking water was provided three times a day. 0.5 ml in 50 ml is 0.01 ml per cc. Each mouse drank approximately 4 ml of water three times a day so each mouse received approximately 0.04 ml of the composition in their drinking water three times a day. Each mouse therefore received approximately a total of 0.04 x 3 = 0.12 ml of the composition from the drinking water each day plus 0.04 ml from the gavage, a total of 0.16 ml per day.

During the trial 4 mice from the experimental group and 5 from the control group died because of the gavage. The mice were all killed on day 17 and the tumours were dissected out and weighed. However, two tumours from the control group could not be removed for measurement because they were too extensive. The results are shown in Table 2.

Table 2

EXPERIMENTAL GROUP		CONTROL GROUP	
Mouse No.	Tumour Weight (g)	Mouse No.	Tumour Weight (g)
1	.10	20	.40
2	.10	21	.50
3	.20	22	.50
4	.20	23	.60
5	.20	24	.60
6	.30	25	.90
7	.30	26	.90
8	.40	27	.90
9	.40	28	1.00
10	.40	29	1.00
11	.50	30	1.00
12	.50	31	1.10
13	.50	32	1.10
14	.50	33	1.30
15	.50	34	1.30
16	.60	35	1.30
17	.70	36	1.50
18	1.00	37	1.70
19	1.70	38	1.80
Average tumour weight	0.48g	39	1.80
		Average tumour weight	1.1

It can be seen from Table 2 that the combined weight of tumours from the experimental group was 9.1 grams. The combined weight of the tumours from the control group was 21.2 grams. The control group tumour mass was therefore 21.2/9.1 = 2.32 times larger than the experimental group tumour mass.

Further, the average tumour weight in the control mice was 1.1 g. The average tumour weight in the experimental mice was 0.48g.

The average control group tumour mass is therefore 1.1/0.48 = 2.29 times larger than the average experimental group tumour mass.

The difference in the size of the tumours as measured by callipers during the trial is shown in Figure 5. It can be seen from Figure 5 that by day 17 the difference in size between the control and experimental tumours, as measured by callipers, is 8.8/3.6 = 2.44 times larger. Again there were no detectable side effects.

Professor Beverley has stated that this experiment has confirmed unequivocally that the treatment causes a statistically highly significant difference in tumour growth between the treated and control mice with no detectable side effects.

EXAMPLE 14

A 30lb 6 year old Manchester Terrier suffering from a spindle cell tumour was treated with the composition described in Example 1.

Before the treatment the animal had a hard lumpy swelling extending over the external side of the left foreleg from below the elbow joint up to the side of the shoulder. This diagnosis was made by Abbey Veterinary Clinics, London, who recommended amputation of the foreleg. 1cc of the composition was administered orally once a day for 5 days. By the end of 5 days the tumour had reduced in size considerably. The dose was then reduced to 1cc on alternate days for a further 7 days.

In addition, an extra 3 g vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 125mg per day.

A dietary regime was followed of organic fruits, organic vegetables, organic grains and lamb's liver to supply essential amino acids. Salt added to food was avoided.

Following the above treatment, the tumour disappeared. This result was

certified by Mr. A. Sebesteny, head vet at the Imperial Cancer Research Fund, Clare Hall Laboratories.

EXAMPLE 15

A 60lb, 11 year old Doberman bitch was treated with a composition consisting of 30 mg copper orotate, 30 mg manganese orotate, 400 mg vitamin C and 3½ ml of an aqueous solution containing 350 mg sodium salicylate, prepared as in Example 1.

The animal was suffering from a urethral obstruction caused by an infiltrating malignant neoplasm thought to be a transitional cell carcinoma. This diagnosis was made at the department of Clinical Veterinary Medicine, Cambridge University. Before the treatment it could pass only a few drops of water with intense straining.

On the first day of treatment, the animal was given 2cc of the above composition (administered orally). On the second day it was given 2cc, followed by 1cc an hour later, then ½cc an hour after that. This was repeated every day for a week, after which time an improvement was noted. The dosage was then reduced to 2cc once a day for a further 3 weeks.

In addition, an extra 6 g vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 250 mg per day. A dietary regime as set out in Example 14 was followed.

Following the above treatment, the animal showed none of the former symptoms. It was still alive and in excellent health 4 years after the treatment, as can be confirmed by its owner.

EXAMPLE 16

An 80lb, 6 year old Alsatian was treated with a composition consisting of 50 mg copper orotate, 50 mg manganese orotate, 50 mg zinc orotate, 400 mg vitamin C and 3½ ml of an aqueous solution containing 350 mg sodium salicylate, prepared in the same way as in Example 1, except that the zinc orotate was mixed dry in finely divided form together with the copper and manganese orotate.

The animal was suffering from a nasal tumour, thought to be a sarcoma and

could not breathe through its nose. This diagnosis was made by the Department of Small Animal Medicine and Surgery, Royal Veterinary College, London. It had a large, hard, golf-ball sized swelling under the right eye.

It was given 2.6cc of the above composition, followed by 1.3cc an hour later (administered orally). This dose was repeated daily for 2 weeks by which time the tumour had significantly regressed, to the extent that the animal could breathe through its nose. The dosage was then reduced to alternate days for a fortnight, then to twice a week, then once a week.

In addition, an extra 8 g vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 330 mg per day.

A dietary regime as set out in Example 14 was followed.

By the end of the above treatment, the animal was symptom free. This result was certified by Mr. A. Sebesteny, head vet at the Imperial Cancer Research Fund.

EXAMPLE 17

A 60lb, 7 year old Doberman dog was treated with the composition described in Example 15. It was suffering from carcinoma of the peritoneum. This diagnosis was made by the Department of Small Animal Medicine and Surgery, Royal Veterinary College, London. The animal was in an emaciated state, with a large swelling on the abdomen.

It was treated with 2cc of the composition, followed by 1cc an hour later (administered orally) every day for two weeks. After two weeks, the dosage was reduced to 2cc per day for a further two weeks, followed by a further reduction to 2cc on alternate days for another two weeks.

In addition, an extra 6 g vitamin C was administered orally each day and nicotinic acid was administered orally in an amount of 250 mg per day.

A dietary regime as set out in Example 14 was followed. After the above treatment the animal was symptom free, as can be confirmed by its owners.

EXAMPLE 18

A 150 lb human male around 45 years old, was treated with the composition

described in Example 15. He was suffering from T-cell lymphoma, diagnosed at the Cromwell Hospital, London.

He was given 4.5cc of the composition (administered orally) once a day for 6 weeks (excluding Sundays). After this time, a regression was noted and the dosage was reduced to alternate days for 2 weeks, followed by a further reduction to once a week for three weeks.

In addition, an extra 15 g of vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 625 g per day.

A dietary regime as set out in Example 14 was followed. Following the above treatment, all symptoms disappeared. He is still alive and well 6 years after the treatment.

CLAIMS

1. A composition comprising:

(a) a physiologically acceptable source of assimilable copper;

(b) a source of salicylic acid or a physiologically acceptable derivative thereof; and

(c) vitamin C.

2. A composition according to claim 1, further comprising (d) a physiologically acceptable source of assimilable manganese.

3. A composition according to claim 1 or 2, further comprising (e) a physiologically acceptable source of assimilable iron and (f) a physiologically acceptable source of assimilable sulfur.

4. A composition according to any one of the preceding claims, further comprising a physiologically acceptable source of assimilable zinc.

5. A composition according to any one of the preceding claims, wherein the said metals are present in the form of salts with organic or inorganic acids.

6. A composition according to any one of the preceding claims, in which components (a) and (b) are present as a copper salicylate complex.

7. A composition according to claim 5, wherein the salts are the same or different and are selected from orotates, aspartates, gluconates, tartrates, citrates, lactates and acetates.

8. A composition according to claim 5 wherein the salts are the same or different and are selected from chlorides, bromides, iodides, phosphates and sulphates.

9. A composition according to any one of the preceding claims wherein the derivative of salicylic acid is sodium salicylate.

10. A composition according to any one of the preceding claims comprising:

(a) 15 to 60 parts by weight copper gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper gluconate is used;

(b) 300 to 600 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other than sodium salicylate is used; and

(c) 200 to 1000 parts by weight vitamin C.

the parts by weight referred to being based on the total weight of these ingredients in the composition.

11. A composition according to claim 10, further comprising 15 to 60 parts by weight manganese gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than manganese gluconate is used.

12. A composition according to claim 10 or claim 11, further comprising 15 to 60 parts by weight of iron gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable iron other than iron gluconate is used, and 15 to 60 parts by weight of sulfur.

13. A composition according to any one of claims 10 to 12, further comprising 15 to 60 parts by weight zinc gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc gluconate is used.

14. A composition according to claim 10, comprising:

(a) 25 to 40 parts by weight copper gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper gluconate is used;

(b) 350 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other than sodium salicylate is used; and

(c) 400 parts by weight vitamin C.

the parts by weight referred to being based on the total weight of these ingredients in the composition.

15. A composition according to claim 14, further comprising 25 to 40 parts by weight manganese gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than

manganese gluconate is used.

16. A composition according to claim 14 or claim 15, further comprising 25 to 40 parts by weight of iron gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable iron other than iron gluconate is used, and 25 to 40 parts by weight of sulfur.

17. A composition according to any one of claims 14 to 16, further comprising 25 to 40 parts by weight zinc gluconate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc gluconate is used.

18. A composition according to any one of the preceding claims for use in the treatment of the human or animal body.

19. Use of a composition according to any one of claims 1 to 17 in the manufacture of a medicament for use in the treatment or prevention of a neoplastic disease.

20. Products containing:

(a) a composition as claimed in any one of claims 1 to 17; and

(b) vitamin C and/or one or more amino acids and/or nicotinic acid,

as a combined preparation for simultaneous, separate or sequential use in the treatment of neoplastic disease.

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(54) Title: PHARMACEUTICAL COMPOSITIONS AND THEIR USE

(57) Abstract: A composition comprising: (a) a physiologically acceptable source of assimilable copper; (b) a source of salicylic acid or a physiologically acceptable derivative thereof; and (c) vitamin C.

Fig.1.

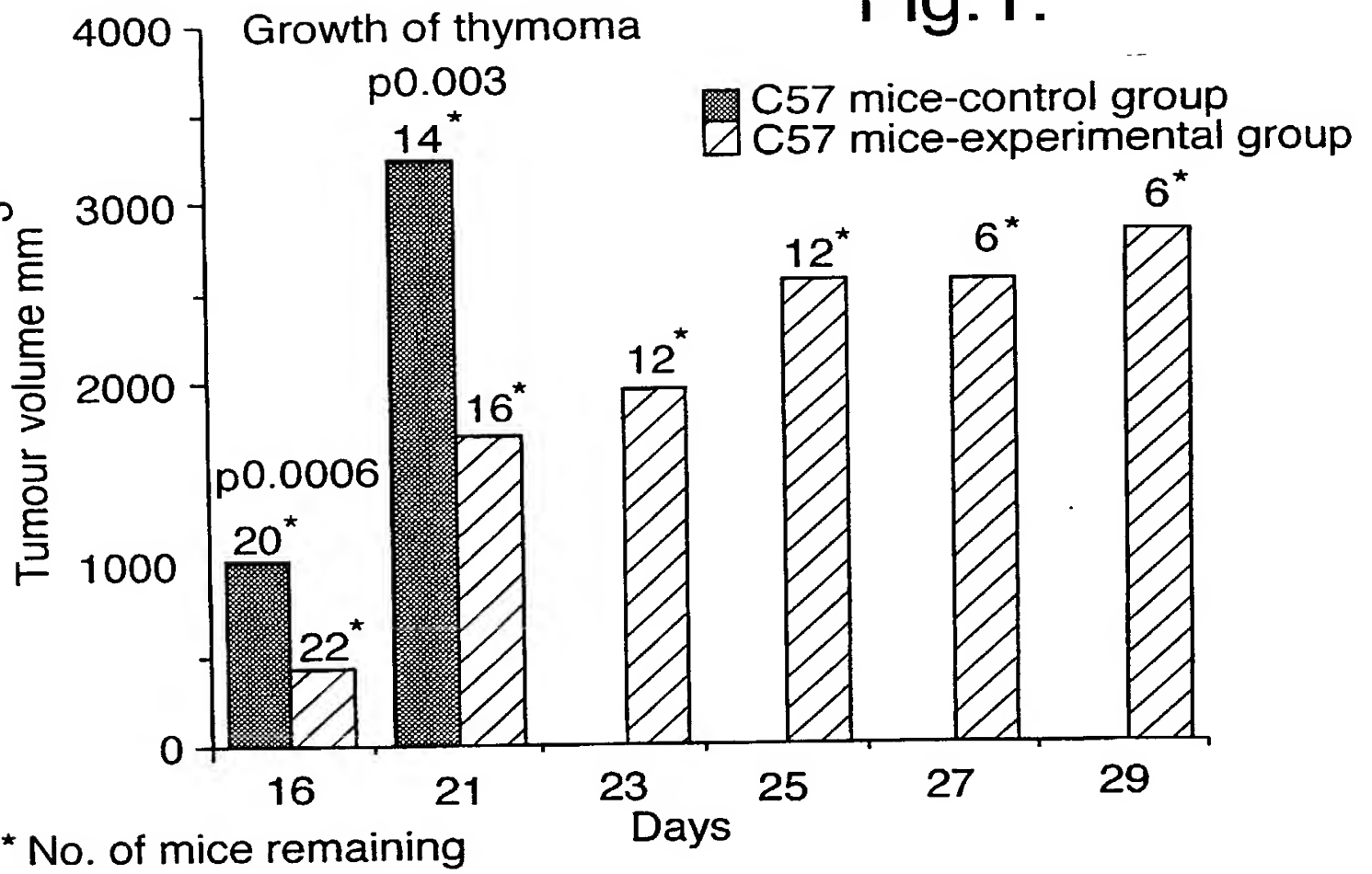

Growth of thymoma
p0.003
p0.0006
C57 mice-control group
C57 mice-experimental group
Tumour volume mm 3
4000
3000
2000
1000
0
20*
22*
14*
16*
12*
12*
6*
6*
16
21
23
25
27
29
Days
* No. of mice remaining

Fig.2.

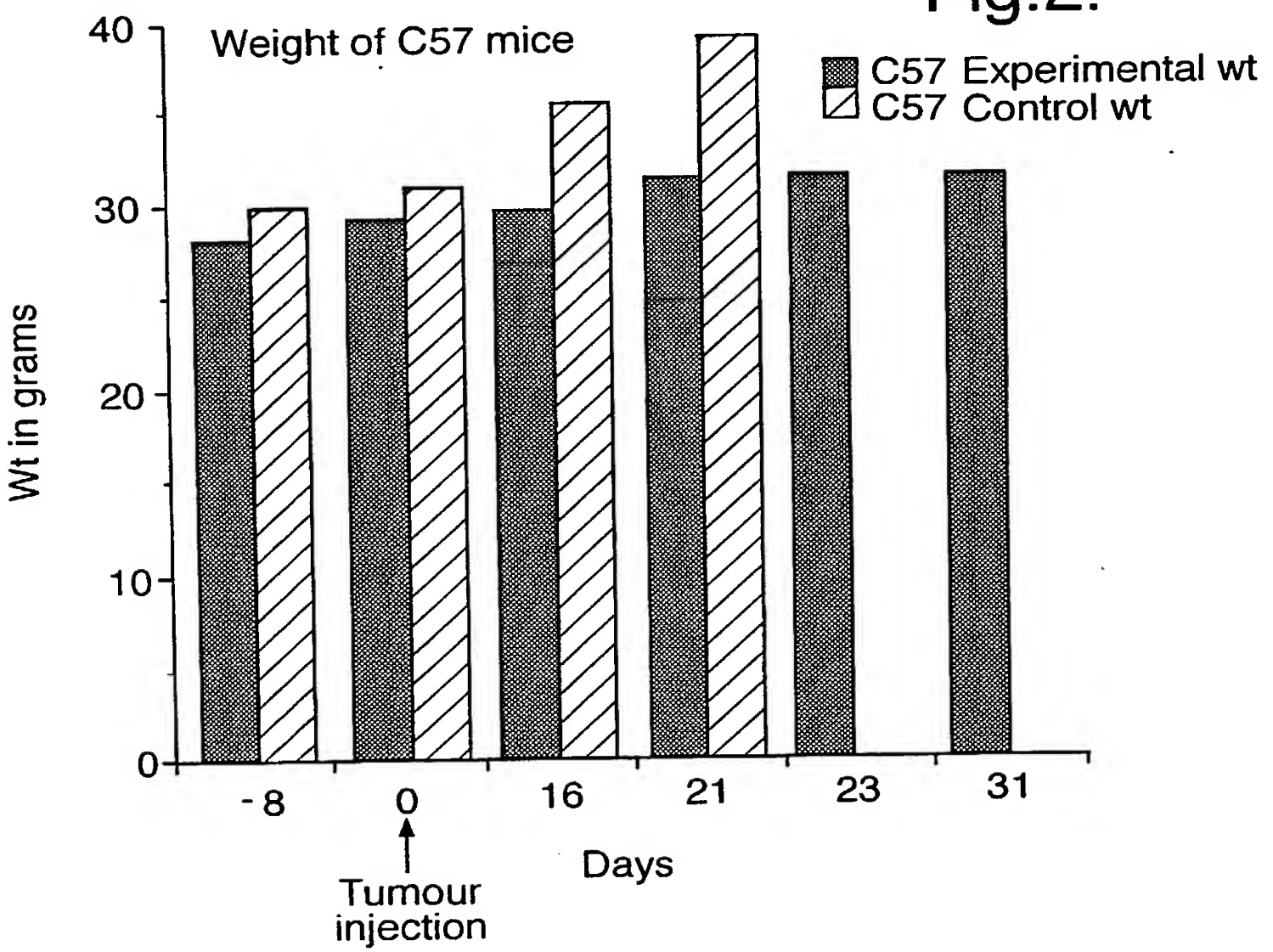
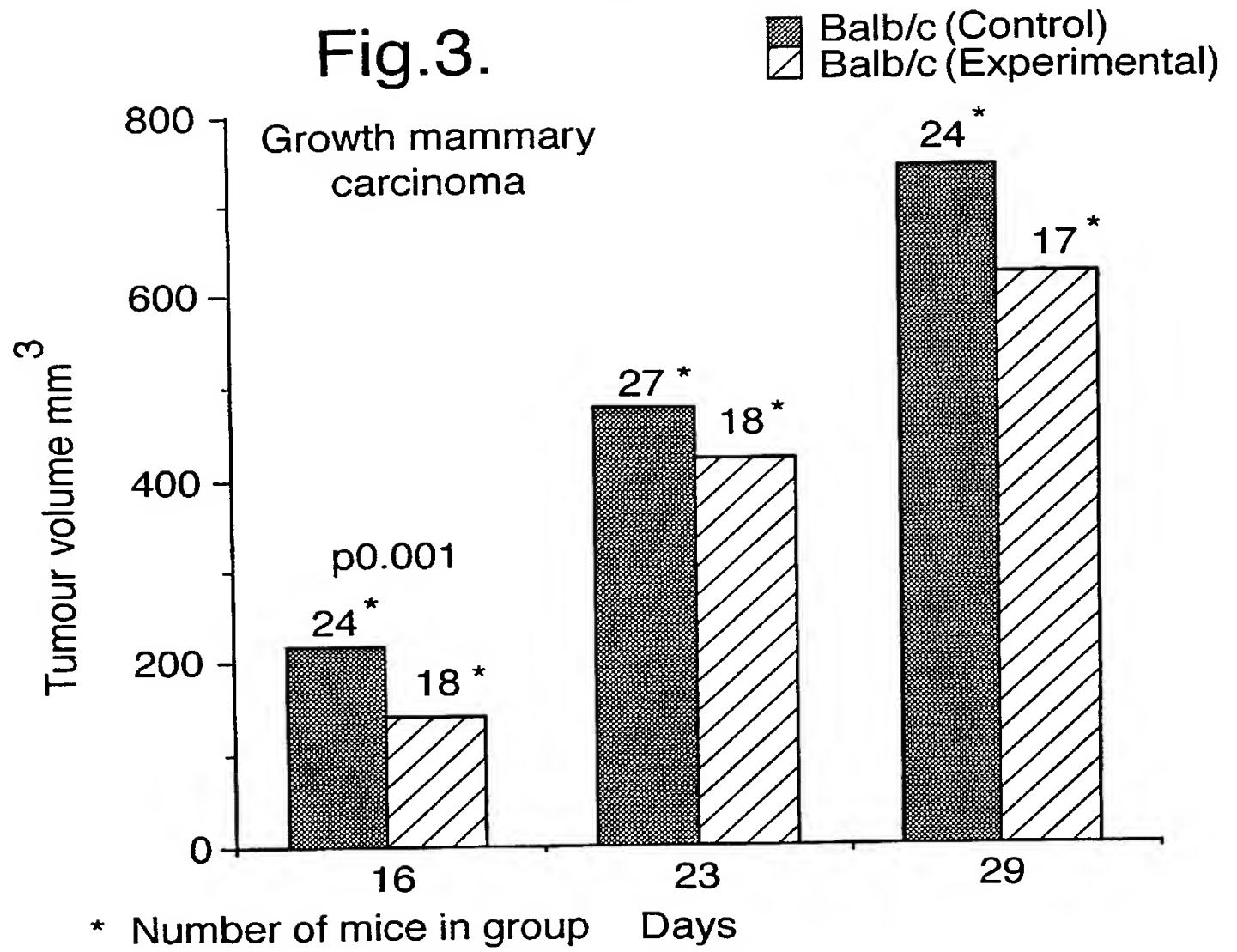
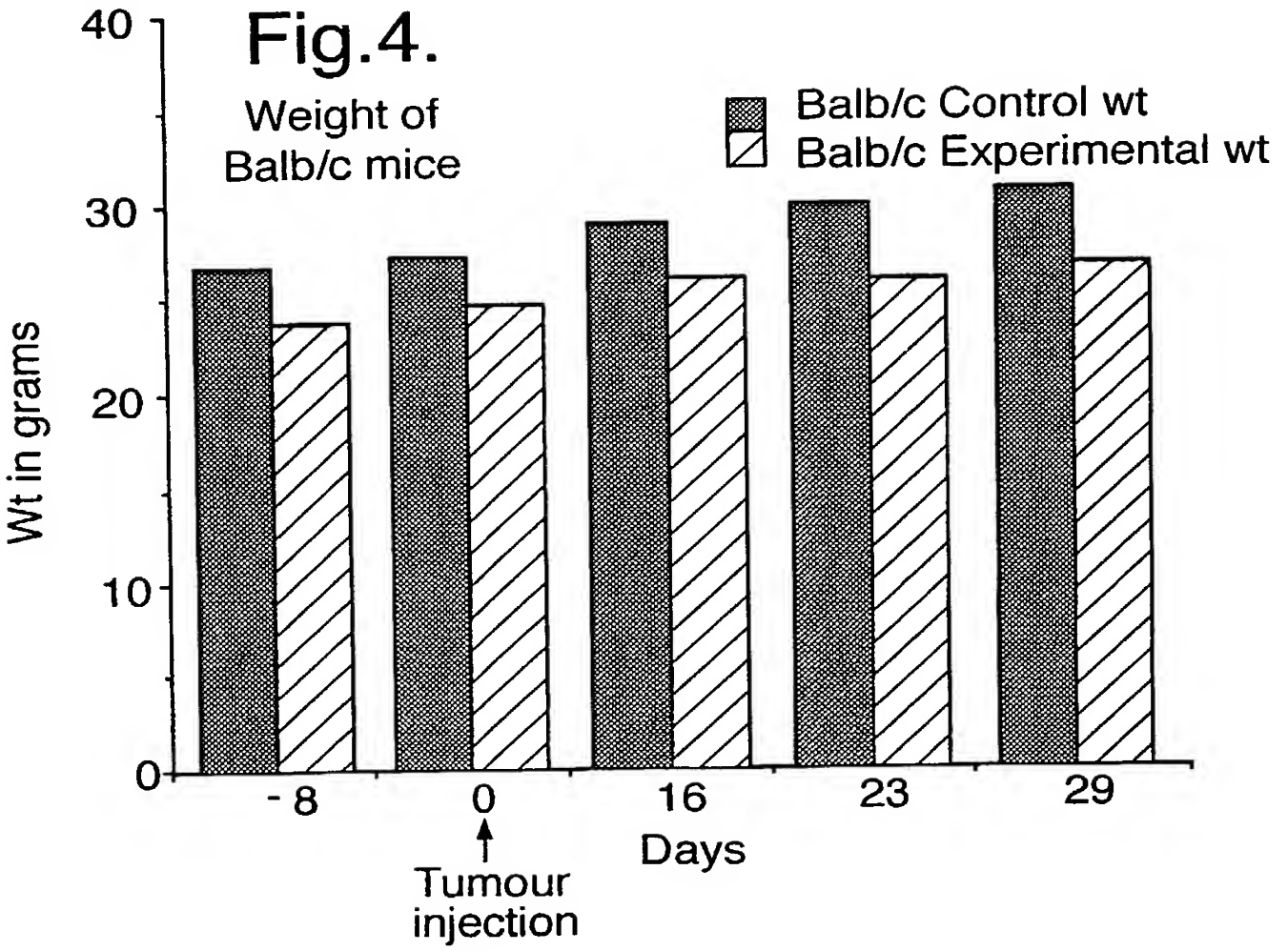

Weight of C57 mice
C57 Experimental wt
C57 Control wt
Wt in grams
40
30
20
10
0
- 8
0
16
21
23
31
Days
Tumour injection

Fig.3.



* Number of mice in group

Fig.4.



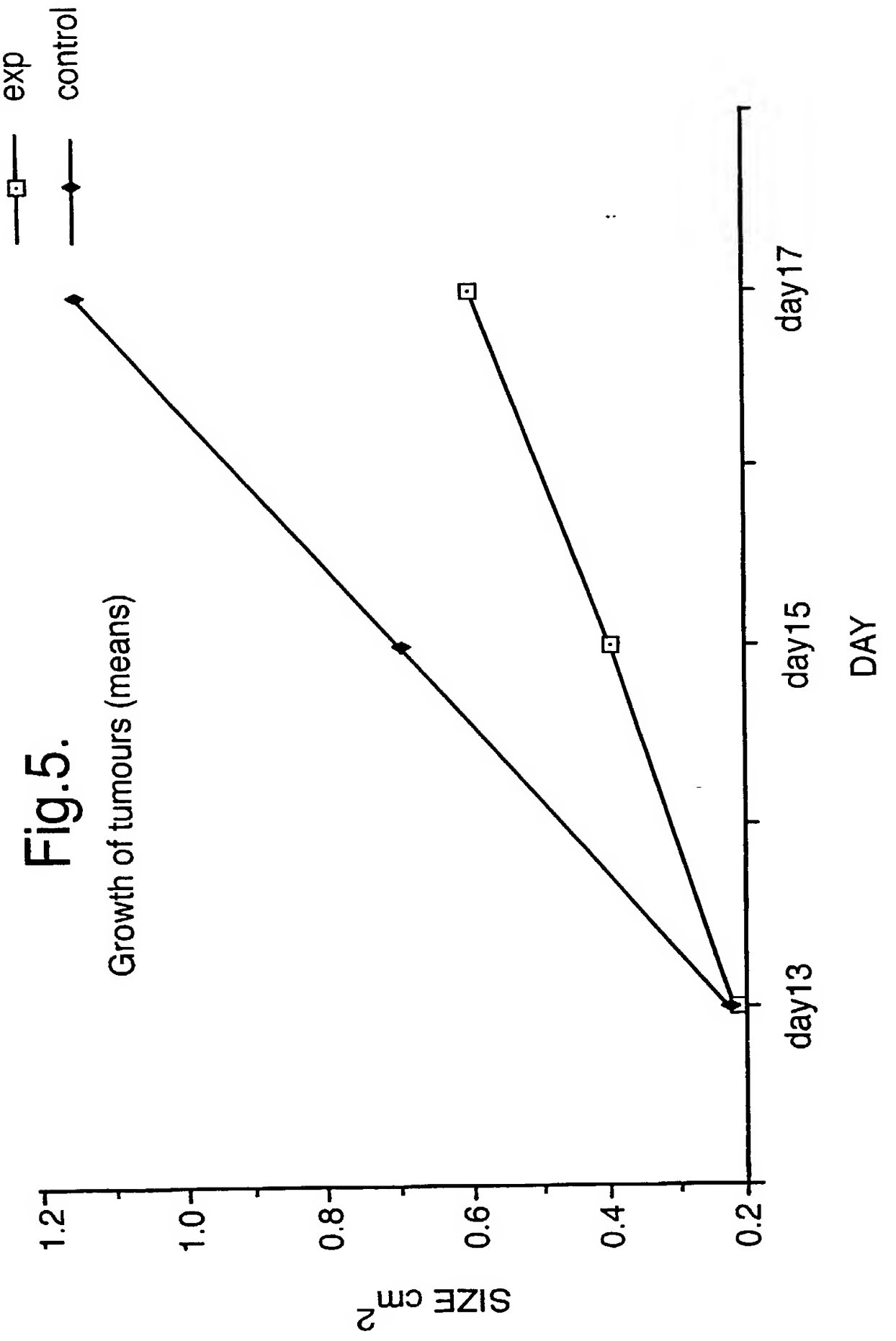

exp
control
day17
day15
day13
DAY
SIZE cm2
1.2
1.0
0.8
0.6
0.4
0.2
Growth of tumours (means)

Fig.5.

COPY

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Insert Title: PHARMACEUTICAL COMPOSITIONS AND THEIR USE IN THE TREATMENT OF NEOPLASTIC DISEASE

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I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representative or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s)			Priority Claimed	
9923431.2 (Number)	GB (Country)	10.04.1999 (Month/Day/Year Filed)	☑ Yes	☐ No
0014420.4 (Number)	GB (Country)	06.13.2000 (Month/Day/Year Filed)	☑ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications(s) listed below.

Insert Provisional Application(s): (if any)

(N/A) (Application Number)	(Filing Date)
(Application Number)	(Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

Insert Requested Information: (if appropriate)

Country	Application Number	Date of Filing (Month/Day/Year)
(N/A)		

I hereby claim the benefit under Title 35, United States Code, §120 of any United States and/or PCT application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States and/or PCT application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Insert Prior U.S. Application(s): (if any)

(N/A) (Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)

Attorney Docket No. 3920-01102

I hereby appoint the practitioners at **CUSTOMER NO. 2292** as my attorneys or agents to prosecute this application and/or an international application based on this application and to transact all business in the United States Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the practitioners, unless the inventor(s) or assignee provides said practitioners with a written notice to the contrary:

Send Correspondence to:

BIRCH, STEWART, KOLASCH & BIRCH, LLP or **CUSTOMER NO. 2292**
P.O. Box 747 • Falls Church, Virginia 22040-0747
Telephone: (703) 205-8000 • Facsimile: (703) 205-8050

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole Inventor: Insert Name of Inventor Insert Date This Document is Signed	GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
	JOHN CARTER	X	X 9/5/02 X
Insert Residence Insert Citizenship →	Residence (City, State & Country) Harrow, Middlesex, UK GBX		CITIZENSHIP BRITISH
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Full Name of Second Inventor, if any: see above	GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
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Full Name of Third Inventor, if any: see above	GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
	Residence (City, State & Country)		CITIZENSHIP
	MAILING ADDRESS (Complete Street Address including City, State & Country)		
Full Name of Fourth Inventor, if any: see above	GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
	Residence (City, State & Country)		CITIZENSHIP
	MAILING ADDRESS (Complete Street Address including City, State & Country)		
Full Name of Fifth Inventor, if any: see above	GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
	Residence (City, State & Country)		CITIZENSHIP
	MAILING ADDRESS (Complete Street Address including City, State & Country)		
Full Name of Sixth Inventor, if any: see above	GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
	Residence (City, State & Country)		CITIZENSHIP
	MAILING ADDRESS (Complete Street Address including City, State & Country)		

*DATE OF SIGNATURE